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PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year)
08 November 2000 (08.11.00)

International application No.
PCT/US00/07680

Applicant's or agent's file reference
110.01270201

International filing date (day/month/year)
22 March 2000 (22.03.00)

Priority date (day/month/year)
22 March 1999 (22.03.99)

Applicant

MCCARTHY, James, B. et al

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
12 October 2000 (12.10.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Henrik Nyberg

Telephone No.: (41-22) 338.83.38

US0007680

MANC

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

1/7/01 Pre Amnd?

To:
Mueting, Raasch, Gebhardt &
Schwappach
Attn. MUETING, A.
P.O. Box 581415
Minneapolis, MN 55458-1415
UNITED STATES OF AMERICA

Date of mailing
(day/month/year) 07/11/2000

Applicant's or agent's file reference
110.01270201

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US 00/07680

International filing date
(day/month/year) 22/03/2000

Applicant
REGENTS OF THE UNIVERSITY OF MINNESOTA et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.


☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority
 European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
Catherine Humbert

RECEIVED

NOV 07 2000

MUETING AND RAASCH

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 110.01270201	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/ 07680	International filing date (day/month/year) 22/03/2000	(Earliest) Priority Date (day/month/year) 22/03/1999
Applicant REGENTS OF THE UNIVERSITY OF MINNESOTA et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of Invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

METHODS OF USE OF BETA 1-INTEGRIN INHIBITORS

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No.

T/US 00/07680

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/06 A61K38/08 A61K38/07 A61P19/00 A61P17/00
 A61P41/00 A61P9/00 A61P35/00 A61P25/00 A61P29/00
 A61K38/39

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, MEDLINE, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>US 5 840 691 A (EVERETT JEFFREY E ET AL) 24 November 1998 (1998-11-24) abstract column 2, line 2 - line 22 column 2, line 30 column 2, line 48 - line 51 column 3, paragraph 49 - paragraph 50 column 9, line 9 - column 10, line 6 claims 1,4-6</p> <p style="text-align: center;">--- -/--</p>	1,4,5,7, 8,32,38



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 "&" document member of the same patent family

Date of the actual completion of the international search

24 October 2000

Date of mailing of the international search report

07/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Noë, V

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>YANAKA KIYOYUKI ET AL: "Neuronal protection from cerebral ischemia by synthetic fibronectin peptides to leukocyte adhesion molecules." JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM, vol. 16, no. 6, 1996, pages 1120-1125, XP000952738 ISSN: 0271-678X cited in the application abstract page 1121, column 1, line 13 - line 26 page 1121, column 2, line 48 - line 49 page 1122, column 1, line 3 - line 6 page 1123, column 1, paragraph 2 - paragraph 3 page 1123, column 2, line 1 - line 6 page 1124, column 1, last paragraph -column 2, paragraph 1 ---</p>	1,4,5,38
X	<p>HINES KEITH L ET AL: "Synthetic fibronectin peptides interrupt inflammatory cell infiltration in transforming growth factor beta-1 knockout mice." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 91, no. 11, 1994, pages 5187-5191, XP002150881 1994 ISSN: 0027-8424 cited in the application abstract page 5187, column 2, paragraph 3 page 5188, column 1, paragraph 3 page 5189, column 1, last paragraph -page 5190, column 2, paragraph 1 page 5191, column 1, last paragraph ---</p>	1,4,5,7,38
X	<p>MOHRI HIROSHI: "Interaction of fibronectin with integrin receptors: Evidence by use of synthetic peptides." PEPTIDES (TARRYTOWN), vol. 18, no. 6, 1997, pages 899-907, XP000952794 ISSN: 0196-9781 page 900, column 2, last paragraph -page 901, column 1, paragraph 3 page 901, column 1, paragraph 6 -column 2, paragraph 1 ---</p>	25
	-/--	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>LEVREY H ET AL: "Induction of fibroblast apoptosis by soluble fibronectin peptides." MOLECULAR BIOLOGY OF THE CELL, vol. 8, no. SUPPL., November 1997 (1997-11), page 181A XP000952737 37th Annual Meeting of the American Society for Cell Biology; Washington, D.C., USA; December 13-17, 1997 ISSN: 1059-1524 abstract</p> <p>----</p>	28-30
A	<p>HUEBSCH JOSEPH C ET AL: "Endothelial cell interactions with synthetic peptides from the carboxyl-terminal heparin-binding domains of fibronectin." CIRCULATION RESEARCH, vol. 77, no. 1, 1995, pages 43-53, XP000952796 ISSN: 0009-7330 abstract page 44, column 2, paragraph 1 - paragraph 2; table 1 page 47, last paragraph -page 48, paragraph 2 page 52, paragraph 2</p> <p>----</p>	25
A	<p>WO 89 01942 A (UNIV MINNESOTA) 9 March 1989 (1989-03-09) abstract page 9, line 3 - line 19 table 3</p> <p>----</p>	
A	<p>PROSPER FELIPE ET AL: "Mobilization and homing of peripheral blood progenitors is related to reversible downregulation of alpha4beta1 integrin expression and function." JOURNAL OF CLINICAL INVESTIGATION, vol. 101, no. 11, 1 June 1998 (1998-06-01), pages 2456-2467, XP002150882 ISSN: 0021-9738 the whole document</p> <p>----</p> <p style="text-align: center;">-/--</p>	35

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/07680

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	CHAPPELL VICKY L ET AL: "Inhibition of leukocyte-mediated tissue destruction by synthetic fibronectin peptide (Trp-9-Tyr)." JOURNAL OF BURN CARE & REHABILITATION, vol. 20, no. 6, November 1999 (1999-11), pages 505-510, XP000952744 ISSN: 0273-8481 abstract page 505, column 2, last paragraph -page 506, column 1, paragraph 2 page 506, column 1, line 37 - line 47 page 509, paragraph 2 -----	1-4,6, 13-20
P,A	WO 99 37669 A (BRIENZO ANGELA ;FURCHT LEO T (US); UNIV MINNESOTA (US); MCCARTHY J) 29 July 1999 (1999-07-29) cited in the application abstract page 2, line 1 - line 18 page 5, line 5 - line 7 page 6, line 11 - line 18 page 6, line 27 - line 9 page 9, line 3 - line 5 -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/07680

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5840691	A	24-11-1998	US 5591719 A	07-01-1997
			EP 0673384 A	27-09-1995
			WO 9413692 A	23-06-1994
			SG 49017 A	18-05-1998
WO 8901942	A	09-03-1989	US 4839464 A	13-06-1989
			US 5019646 A	28-05-1991
			AT 87936 T	15-04-1993
			AU 605637 B	17-01-1991
			AU 2385988 A	31-03-1989
			CA 1305084 A	14-07-1992
			DE 3880139 D	13-05-1993
			DE 3880139 T	21-10-1993
			EP 0366728 A	09-05-1990
			JP 2690767 B	17-12-1997
			JP 3500046 T	10-01-1991
			US 5116368 A	26-05-1992
			US 5171271 A	15-12-1992
			US 5147797 A	15-09-1992
			US 5294551 A	15-03-1994
			ZA 8806314 A	26-04-1989
WO 9937669	A	29-07-1999	NONE	

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MUETING, Ann M.
MUETING, RAASCH & GEBHARDT, P.A.
P.O. Box 581415
Minneapolis, MN 55468-1415
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing
(day/month/year) 10.04.2001

Applicant's or agent's file reference
110.01270201

IMPORTANT NOTIFICATION

International application No.
PCT/US00/07680

International filing date (day/month/year)
22/03/2000

Priority date (day/month/year)
22/03/1999

Applicant
REGENTS OF THE UNIVERSITY OF MINNESOTA et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

RECEIVED

APR 19 2001

MUETING AND RAASCH

Name and mailing address of the IPEA/

 European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Hundt, D

Tel. +49 89 2399-8042




PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 110.01270201	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/07680	International filing date (day/month/year) 22/03/2000	Priority date (day/month/year) 22/03/1999
International Patent Classification (IPC) or national classification and IPC A61K38/06		
Applicant REGENTS OF THE UNIVERSITY OF MINNESOTA et al.		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 12 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 33 sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input checked="" type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input checked="" type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input checked="" type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 		
Date of submission of the demand 12/10/2000	Date of completion of this report 10.04.2001	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fayos, C Telephone No. +49 89 2399 2180	



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/07680

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*

Description, pages:

1-5,9,11-13,17-20, as originally filed
26,27,35,37

6-8,10,14-16,21-25, with telefax of 29/03/2001
28-34,36

Claims, No.:

1,2,4-11,13,14,17-22, as originally filed
25,26,28,29,31-33,
35,36,38,39

3,12,15,16,23,24, with telefax of 29/03/2001
27,30,34,37,40

Drawings, sheets:

1/16-5/16,7/16-10/16, as originally filed
15/16

6/16,11/16-14/16, with telefax of 29/03/2001
16/16

Sequence listing part of the description, pages:

1-6, filed with the letter of 11.07.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/07680

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

see separate sheet

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

- ☐ copy of the earlier application whose priority has been claimed.
- ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/07680

- ☒ claims Nos. 1-40 (industrial applicability).

because:

- ☒ the said international application, or the said claims Nos. 1-40 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:
- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.
2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
- ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/07680

- ☒ all parts.
- ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-3, 6, 9-31, 33-37 and 39-40
	No:	Claims	1, 4, 5, 7, 8, 32 and 38
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-40
Industrial applicability (IA)	Yes:	Claims	1-40 see separate sheet
	No:	Claims	-

2. Citations and explanations see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/07680

Re Item I

Basis of the opinion

- 1- Sequence listing pages 1-6 filed with the letter of 11.07.2000 do not form part of the application (Rule 13^{ter}.1(f) PCT).

Re Item II

Priority

- 2- The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that is not correct, the documents D9 and D10 cited in the international search report could become relevant.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

- 3- Claims 1-40 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 4- Reference is made to the following documents:

- D1: US-A-5 840 691 (EVERETT JEFFREY E ET AL) 24 November 1998 (1998-11-24)
- D2: YANAKA KIYOYUKI ET AL: 'Neuronal protection from cerebral ischemia by synthetic fibronectin peptides to leukocyte adhesion molecules.' JOURNAL OF

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/07680

CEREBRAL BLOOD FLOW AND METABOLISM, vol. 16, no. 6, 1996, pages 1120-1125, XP000952738 ISSN: 0271-678X cited in the application

- D3: HINES KEITH L ET AL: 'Synthetic fibronectin peptides interrupt inflammatory cell infiltration in transforming growth factor beta-1 knockout mice.' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 91, no. 11, 1994, pages 5187-5191, XP002150881 1994 ISSN: 0027-8424 cited in the application
- D4: MOHRI HIROSHI: 'Interaction of fibronectin with integrin receptors: Evidence by use of synthetic peptides.' PEPTIDES (TARRYTOWN), vol. 18, no. 6, 1997, pages 899-907, XP000952794 ISSN: 0196-9781
- D5: LEVREY H ET AL: 'Induction of fibroblast apoptosis by soluble fibronectin peptides.' MOLECULAR BIOLOGY OF THE CELL, vol. 8, no. SUPPL., November 1997 (1997-11), page 181A XP000952737 37th Annual Meeting of the American Society for Cell Biology; Washington, D.C., USA; December 13-17, 1997 ISSN: 1059-1524
- D6: HUEBSCH JOSEPH C ET AL: 'Endothelial cell interactions with synthetic peptides from the carboxyl-terminal heparin-binding domains of fibronectin.' CIRCULATION RESEARCH, vol. 77, no. 1, 1995, pages 43-53, XP000952796 ISSN: 0009-7330
- D7: WO 89 01942 A (UNIV MINNESOTA) 9 March 1989 (1989-03-09)
- D8: PROSPER FELIPE ET AL: 'Mobilization and homing of peripheral blood progenitors is related to reversible downregulation of alpha4beta1 integrin expression and function.' JOURNAL OF CLINICAL INVESTIGATION, vol. 101, no. 11, 1 June 1998 (1998-06-01), pages 2456-2467, XP002150882 ISSN: 0021-9738
- D9: CHAPPELL VICKY L ET AL: 'Inhibition of leukocyte-mediated tissue destruction by synthetic fibronectin peptide (Trp-9-Tyr).' JOURNAL OF BURN CARE & REHABILITATION, vol. 20, no. 6, November 1999 (1999-11), pages 505-510, XP000952744 ISSN: 0273-8481
- D10: see item VI

NOVELTY - Art. 33 (1) and (2) PCT

5- Claims 1, 4, 5, 7, 8, 32 and 38 lack novelty for the following reasons:

- 5.1- D1 (see e. g. c 2) relates to a method for treating conditions associated with inflammatory diseases (see c 9 lines 10-47), by administering to the patient an effective amount of a composition containing a polypeptide or mixture of polypeptides having the formula: WQPPRARL corresponding to an isolated region of fibronectin residues and capable of interacting (inhibiting) with β 1-integrin.

Therefore, in the light of D1, claims 1, 4, 5, 7, 8 and 38 lack novelty.

- 5.2- D2 discloses the use of fibronectin peptides (Trp-Gln-Pro-Pro-Arg-Ala-Arg-Ile) (p 1121 c 2 last § - p 1122 c 1 § 1) for inhibiting the infiltration of leukocytes into ischemic tissue, reducing the size of infarction and reducing neurological dysfunction after transient focal cerebral ischemia in rats (p 1123 c 2 § 1 and p 1124 c 1 last § - c 2).

In the light of D2, claims 1, 4, 5, 7, 8 and 38 are therefore not novel.

- 5.3- D3 the use of fibronectin peptides (Trp-Gln-Pro-Pro-Arg-Ala-Arg-Ile - p 5188 c 1 § 3) for blocking leukocyte recruitment and pathology in tissues (p 5187 c 2 § 3).

Hence, D3 destroys the novelty of claims 1, 4, 5, 7, 8 and 38.

6- Claims 2-3, 6, 9-32, 33-37 and 39-40 appear to be novel over the prior art cited in the search report.

- 6.1- The novel features are
- The β 1-integrin inhibitor is a peptide comprising a C-terminal LipAr motif,
 - the use of a β 1-integrin inhibitor for treating burn/burn-type injuries,
 - the use of a β 1-integrin inhibitor for treating cancer,
 - the use of a β 1-integrin inhibitor for treating osteoporosis, and

- the use of a β 1-integrin inhibitor for peripheralizing stem cells.

INVENTIVE STEP - Art. 33 (1) and (3) PCT

- 7- The problem posed in the present application is to provide means for inhibiting integrin activity in pathological conditions.

The solution proposed in the present application is the use of a β 1-integrin inhibitor.

The closest prior art is represented by D1, D2 and/or D3 which report the use of a β 1-integrin inhibitor for blocking leukocyte recruitment and pathologies in tissues.

8- Claims 1-40 lack inventive step for the following reasons:

- 8.1- The addition of a C-terminal LipAr motif to the β 1-integrin inhibitor is not explicitly suggested in the available prior art. However, the addition of a C-terminal LipAr motif does not appear from the present description to provide any technical effect of the β 1-integrin inhibitor in comparison with the β 1-integrin inhibitor disclosed in the available prior art.

Burn and burn-type injuries are merely two of several clinical situations that share an inflammation-mediated progression of injury size and scope, and hence the use of a β 1-integrin inhibitor for treating burn /burn-type injuries is not inventive since the use of β 1-integrin inhibitors for treating conditions associated with inflammatory diseases is well known (see e. g. D1, D2 and/or D3).

The use of a β 1-integrin inhibitor for treating cancer is suggested by e. g. D4 (see e. g. p 900 c 2 § 2 - p 901 c 1 § 3).

Osteoporosis is merely one of several clinical situations that share an inflammation-mediated progression of injury size and scope, and hence the use of a β 1-integrin inhibitor for treating osteoporosis injuries is not inventive since the use of β 1-integrin

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/07680

inhibitors for treating conditions associated with inflammatory diseases is well known (see e. g. D1, D2 and/or D3).

The use of a β 1-integrin inhibitor for peripheralizing stem cells is suggested by e. g. D8 (see e. g. discussion p 2463 - 2465).

Therefore, the subject matter of claims 1-40 lacks inventive step in the light of the prior art cited in the search report.

INDUSTRIAL APPLICABILITY - Art. 33 (1) and (4) PCT

- 9- For the assessment of the present claims 1-40 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

- 10- Certain published documents (Rule 70.10): D10

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 99/37669	29.07.99	21.01.99	22.01.98 12.08.98

Re Item VIII

Certain observations on the international application

- 11- The subject matter of claims 25-40 (i. e. use of a β 1-integrin inhibitor for the

treatment of cancer, osteoporosis and for peripheralizing stem cells) is not supported by the technical contents of the description as required by Article 6 PCT.

Re Item IV

Lack of unity of invention

FOR THE SAKE OF COMPLETENESS, NOTE THAT:

12- This Authority found that the requirement of unity of invention is not complied with for the following reasons:

12.1- The common concept linking independent claims 1, 7, 13, 21, 25, 28, 32 and 35 is the use of a β 1-integrin inhibitor for inhibiting integrin activity in pathological conditions. This concept is neither novel, nor inventive (see e. g. D1-D4 and D8).

12.2- Therefore, claims 1, 7, 13, 21, 25, 28, 32 and 35 are not so linked as to form a single general inventive concept (Rule 13.1 PCT) and give rise to the following separate inventions or groups of inventions:

Invention 1: A composition comprising a β 1-integrin inhibitor and its use of a β 1-integrin inhibitor for inhibiting inflammatory leukocyte mediated destruction of tissue (claims 1-6 and 38-40)

Invention 2: A composition comprising a β 1-integrin inhibitor and its use of a β 1-integrin inhibitor for treating a stroke patient (claims 7-12 and 38-40)

Invention 3: A composition comprising a β 1-integrin inhibitor and its use of a β 1-integrin inhibitor for treating a patient having a burn-type injury and/or a burn patient (claims 13-24 and 38-40)

Invention 4: A composition comprising a β 1-integrin inhibitor and its use of a β 1-integrin inhibitor for treating a cancer patient (claims 25-31 and 38-40)

Invention 5: A composition comprising a β 1-integrin inhibitor and its use of

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/07680

a β 1-integrin inhibitor for treating a patient for osteoporosis
(claims 32-34 and 38-40)

Invention 6: A composition comprising a β 1-integrin inhibitor and its use of
a β 1-integrin inhibitor for peripheralizing stem cells (claims 35-
37 and 38-40)

12.3- Despite the aforementioned objection, according to Rule 68.1 PCT, this
Authority has chosen not to invite the applicant to restrict the claims or pay
additional fees.